REMARKS

Claims 1-21 are currently pending in the application. Claims 10 and 12 are presently withdrawn by the Examiner, although reconsideration is requested as discussed below. Claims 1-3, 8, 9 and 20 are amended. Claim 4 is cancelled without prejudice. The amendments find support in the specification and are discussed in the relevant sections below. No new matter is added.

Election/Restrictions:

The Office Action states that claims 10 and 12 are directed to an invention that is independent or distinct from the invention originally claimed. Specifically, the Office Action states

> "Claim 1 is drawn to a method comprising (a) providing a virus encoding and displaying a fusion polypeptide which comprises a polypeptide, a viral coat protein, and a cleavable site, (b) exposing the virus to a cleaving agent, (c) propagating the virus comprising intact fusion protein. However, claim 10 states that members of the repertoire of phage displayed fusion proteins are partially unfolded and therefore susceptible to cleavage. The specification clearly teaches that "the cleavable site is advantageously located in or adjacent to the heterologous polypeptide such that it can be protected by folding of the heterologous polypeptide and thus allow selection for heterologous polypeptides which are capable of correct folding" (please refer to page 6, lines 20-22). The specification also clearly states that the fusion polypeptide "if cleaved will result in the impairment of infectivity" (please refer to page 9, lines 19-20). Therefore, the partially unfolded polypeptide of present claim 10 can not be propagated and does not comprise intact fusion protein (please refer to present claim 1). Moreover, claim 12 states that the exposing step (i.e., step (b) of present claim 1) is undertaken in the presence of a protein denaturant. The presence of a protein denaturant would cause the protein to unfold and be susceptible to cleavage. Therefore, the unfolded fusion polypeptide of present claim 12 would be cleaved and no longer be "intact" and could not be propagated.
>
> This invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 10 and 12 are withdrawn from consideration as being directed to a non-elected invention."

Applicants respectfully disagree. Applicants submit that the claimed methods exploit the application of peptide cleavage to eliminate unwanted viruses in a repertoire of viruses (see the

specification at page 3, lines 6-7). Using the claimed selection methods, virus may be selected from a repertoire of viruses by cleavage of non-resistant virions using a cleaving agent (see specification at page 3, lines 18-19). In all claimed methods, the uncleaved polypeptides are selected for; the cleaved material is discarded in the selection step. (see specification at page 6, lines 1-3). Cleavage of displayed polypeptides in the claimed methods results in impairment of the viruses to achieve infection of host cells. Thus, by propagating viruses which have been exposed to a cleavage agent, it is possible to enrich the population for virions which comprise displayed polypeptides that are *resistant* to cleavage, and therefore more likely to be correctly folded. That is, cleavage selects against virions displaying incorrectly folded fusion polypeptide and for those displaying correctly folded fusion polypeptide. The specification specifically provides for adjustment of the stringency or sensitivity of the selection by exposing the virions to cleavage agent under conditions which modulate the lability of the cleavage site. See, for example, page 11, line 21 to page 12, line 18. Particularly relevant portions of this description are copied below for convenience:

> The invention optimally comprises the use of conditions or agents, during cleavage of the cleavable site, which *modulate the lability of the cleavage site in the presence of the cleaving agent*. This approach may be used to *increase cleavage, for example to select only for polypeptides which fold in such a manner as to closely shield the cleavable site from access by the cleaving agent*, or to decrease cleavage, for example, to select stable mutants from a repertoire of polypeptides which is ordinarily relatively labile under cleavage conditions.
>
> For example, modulation of the lability of the cleavable site may be achieved by the *use of agents which increase or decrease such lability*. Thus, a *protein denaturant may be included,* at a suitable concentration, *to destabilize a polypeptide and render it more labile.* ..... Alternatively the ligand may destabilize the folded structure of the polypeptide, for example, by favouring the adoption of an alternative configuration. This may render the polypeptide more accessible to the cleavage agent, and thus more labile.
>
> In a further embodiment, the conditions of the cleavage process may be altered, such as by manipulating the pH or the temperature at which cleavage is conducted, to achieve similar effects. Thus, *deviation of the pH from the optimum for the polypeptide comprising the cleavable site may cause the site to become more accessible to the cleaving agent*. Similarly, raising (or lowering) the temperature of the conditions under which the polypeptide is cleaved may render the polypeptide more or less susceptible to cleavage.

> In some instances, non-covalent interactions may be responsible for peptides retaining their structure and coat proteins remaining viable, even after the successful cleavage of the cleavable site. *The use of denaturants, temperature variation and other potentially destabilizing techniques may also be used to decrease the likelihood of a cleaved polypeptide retaining its structure.* (Emphases added.)

In view of these teachings that the susceptibility to cleavage can be modulated to "increase cleavage, for example to select only for polypeptides which fold in such a manner as to closely shield the cleavable site from access by the cleaving agent," it is clear that undertaking cleavage "under conditions at which some members of the repertoire are at least partially unfolded," as recited in claim 10 is a method of adjusting the sensitivity of the selection. Cleavage under these conditions will select more stringently for repertoire members that are stably folded. Obviously, if cleavage under these conditions results in cleavage of all viroins such that no virus is propagated, as suggested by the Office Action, there would be no selection at all and there is no point in the method. However, as described in the specification as noted above, the point of performing cleavage "under conditions at which some members of the repertoire are at least partially unfolded" (as recited in claim 10) or "in the presence of a protein denaturant" (as recited in claim 12) is to modulate the sensitivity of the selection. Performing the selection under partially unfolding or mildly denaturing conditions will increase the sensitivity of the selection for members in which the fusion polypeptide is more stably folded, i.e., resistant to unfolding or denaturation.

In view of the above, Applicants submit that claims 10 and 12, especially when read in light of the specification, still select for intact fusion protein – i.e., all virions are not necessarily cleaved - and exposure to cleavage agent does not result in propagation of no virus, as concluded in the Office Action. Applicants therefore request reconsideration of the withdrawal of claims 10 and 12 as being drawn to a non-elected invention.

Priority:

The Office Action acknowledges Applicants' claim for foreign priority based on three applications filed in the UK, but notes that Applicant has not filed a certified copy of the PCT (PCT/GB99/01526, filed May 13, 1999) or the GB applications (9810223.9 and 9810228.8) as

required by 35 U.S.C. §119(b). Applicants submit that the PCT application designates the U.S. and is therefore a U.S. application for priority purposes – a certified copy of the PCT is not required. Certified copies of the GB applications are submitted herewith.

The Office Action also denies Applicants' claim for priority from UK application Nos. 9810228.8 and 9810223.9, both filed May 13, 1998 because "a claim for priority under 35 U.S.C. §119(a)-(d) cannot be based on said application since the United States application was filed more than twelve months thereafter. Applicants respectfully disagree.

Applicants submit that the present U.S. application is a continuation, under 35 U.S.C. §120, of PCT/GB99/01526, filed May 13, 1999, which designated the U.S. and is, for priority purposes, a U.S. application. The PCT filed May 13, 1999 was filed within twelve months from the two GB applications, filed May 13, 1998. Because the PCT was a U.S. application filed within twelve months of both GB applications, the PCT is entitled to the priority of the GB applications. Further, because the PCT was a U.S. application for priority purposes, the present U.S. application, which claims priority from the PCT application under §120, and was filed during the pendency of the PCT application, is entitled to the priority of the PCT application and thus to the priority of the GB applications. Applicants respectfully request acknowledgment of the priority claim.

Oath/Declaration:

The Office Action states that the Declaration is defective because "non-initialed and/or non-dated alterations have been made to the oath or declaration," and because "the declaration states that 'this declaration is for a national stage of PCT application,' however, the current application is not a '371." The Office Action also states that "the declaration states that the country of citizenship is 'French' or 'British' which are not countries, but nationalities."

Applicants submit that it is clear from the non-executed version of the declaration filed with the original filing papers that the line-through in inventor Kristensen's address is lined through before the inventor's signature and dating. Nonetheless, Applicants submit herewith a

non-executed replacement Declaration addressing all issues raised. An executed version will be filed in a supplemental filing as soon as it is available.

Specification:

The specification is objected to for several reasons. First, the Office Action copies the provisions of 37 C.F.R. §1.77(b) regarding the arrangement of the specification. Applicants note that 37 C.F.R. §1.77(b) states that "the specification of a utility application *should* include the following sections in order." Applicants submit that this is not a requirement for a specific format.

The disclosure is objected to for informalities as noted below. Each has been amended in the "Amendments to the Specification" herein above. The amendments add no new matter.

On page 9, line 25, the phrase "the viral will" has been changed to "the virus will" as suggested.

On page 12, line 32, the phrase "cleavable site on to near to an associated tag" has been corrected to "cleavable site on or near to an associated tag."

On page 15, line 1, "GndHCl" is modified to recite "GndHCl (Guanidine Hydrochloride)" so the full name appears at the first use of the abbreviation.

On page 17, Table 1 has been modified to refer to pH, rather than PH.

On page 18, line 10, the phrase "express fusion protein" is correct in the present tense, as the phrase is referring to "consistent with indications." No change is believed necessary.

On page 37, line 25, the phrase "a^{32}P-dCTP" is corrected to "α^{32}P-dCTP."

A replacement page for page 39 is submitted herewith to correct the skewing of the text.

A replacement Sequence Listing is submitted herewith, showing an entry for the amino acid sequence AGGAAA. The Specification has been amended at page 40, line 4 to include a SEQ ID NO identifier for this sequence.

The Office Action noted that it is well known in the art that pIII, p3, g3 and gene III are abbreviations for coat protein III, the use of several different abbreviations for the same term in one application is somewhat confusing. The Office Action states that "a definition of the coat protein with appropriate abbreviations would clarify the issue." Applicants have amended the specification at page 8 to state "As used herein, the terms pIII, p3, g3 and gene III are equivalent alternative abbreviations for bacteriophage coat protein III." The amendment adds no new matter.

Finally, the Office Action notes that the trademarks Pefabloc, Sculptor and ECL are used in the specification. The trademark terms have been capitalized and are accompanied by the generic terminology in the specification as amended.

Claim Objections:

Claim 2 is objected to for recitation of the phrase "in wherein the cleavage site is located.." The claim is amended herein to recite simply "wherein the cleavable site is located..." The amendment adds no new matter.

Rejections under 35 U.S.C. §112, First Paragraph:

Claim 1 and all dependent claims are rejected under 35 U.S.C. §112, first paragraph for lack of written description. The Office Action states:

> The claimed invention states that a fusion polypeptide with a cleavable site will be exposed to a cleaving agent and then an **intact** fusion polypeptide will be propagated. The claimed invention does not include any structural information regarding the fusion polypeptide except that the fusion polypeptide contains a cleavable site. In addition, the claimed invention does not include any structural information regarding how a displayed polypeptide displaying a cleavable site would be exposed to a cleaving agent and still remain intact. The structural limitation that the fusion polypeptide must be properly folded in order for propagation of virus comprising intact fusion protein is not present in the claimed invention. Furthermore the specification does not teach how virus exposed to a cleaving agent could be propagated. Is the virus resistant to cleavage by the cleaving agent? Can the virus actually propagate after exposure to the cleaving agent?

The Office Action thus concludes that the invention as claimed fails to satisfy the written description requirement. Applicants respectfully disagree.

Claim 1 as amended requires that "a virus comprising a plurality of virions"...."comprises a cleavable site located within a displayed polypeptide" and that "cleavage of said cleavable site impairs infection by a said virion." The language "virus comprising a plurality of virions" is supported, for example, at page 3, lines21-22 which state "Thus, 'virus' may refer to a plurality of virions, such that it may encode a repertoire of polypeptides." The language regarding impairment of infection is supported on page 8, lines 16-21. The impairment of infection caused by cleavage is taught to "enrich the virus for virions which comprise displayed polypeptides which are resistant to cleavage" in order to "reduce background attributable to phage displaying no heterologous polypeptides, or phage displaying heterologous polypeptides which are incapable of folding correctly." See page 8, lines 14-16 and 18-20.

The claim as amended also requires that the cleaving agent "only cleaves said cleavable site if said fusion polypeptide is not properly folded," such that exposure of the virus comprising the plurality of virions to the cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded." Thus, the claim as amended specifically recites a basis for the selection, i.e., virions displaying a fusion protein that is not properly folded are selected against. Such selection therefore leaves those virions in the recited virus comprising a plurality of virions that display folded fusion protein intact and able to be propagated as recited in step (c) of the amended claim.

Claim 1 as amended includes the limitations that "cleavage of said cleavable site impairs infection by a said virion" and that "the cleaving agent only cleaves the cleavable site if said fusion polypeptide is not properly folded." The Office Action acknowledges that the specification provides written description support for "virus displaying a polypeptide correctly folded to protect from cleavage." The specification also states, regarding the cleavable site in the fusion polypeptide that it "can be protected by folding of the heterologous polypeptide and thus allow selection for heterologous polypeptides which are capable of correct folding." (page 6,

lines 21-22) Further, as noted above, the specification teaches at page 6, lines 1-3 that "In all embodiments of the present invention..... the uncleaved polypeptides are selected for; the cleaved material is discarded in the selection step." Thus, the specification supports the recited requirement that the exposure to cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded."

It is noted that the claim initially recited "virus" rather than "virus comprising a plurality of virions." The term "virus" as initially used is intended to encompass more than one virion, such that cleavage does not necessarily mean that the only virus is cleaved and no virus can be propagated. Support for this interpretation of the meaning of "virus" is found at, for example, page 3, lines 21-22 as noted above, and, for example, at page 8, lines 18 to 20, which recite "Thus, by propagating viruses which have been exposed to a cleavage agent, it is possible to *enrich the virus for virions* which comprise displayed polypeptides which are resistant to cleavage" (emphasis added). Also, at page 6, lines 5 and 6 the specification states "Preferably the *virus* according to the invention *encode a repertoire* of heterologous polypeptides." That is, the term "virus" is intended as and used to encompass a plural noun, i.e., the term "virus" encompasses the plural "virions." Thus, where the term "virus" is used, it is not referring only to a single viral particle, and cleavage of "virus" does not mean that *all* virions in the population are cleaved and no propagation can occur. (Applicant notes that the Office Action apparently acknowledges that "virus" encompasses plural virions on, for example page 12, where it states "The omitted steps are: Selecting virus which *are* resistant to cleavage...." (emphasis added). If "virus'" is referring to singular virions only, the Office Action should have recited "Selecting virus which *is* resistant to cleavage" or "Selecting a virus which is resistant to cleavage.") The plain language of the initial claim required that "virus comprising intact fusion protein" is present to be propagated. Nonetheless, in order to make it abundantly clear that the claim is referring to more than one viral particle, the claim has been amended to refer to "virus comprising a plurality of virions" encoding and displaying a fusion polypeptide. It is the "virus" which comprises "a plurality of virions" that is exposed to a cleaving agent in step (b), and the claim as amended refers to the propagation of "a virion" (i.e., at least one) comprising intact fusion polypeptide.

In view of the amendment to specifically require "a virus comprising a plurality of viruses" and to require that the cleaving agent only cleaves the cleavable site "if the fusion polypeptide is not properly folded," such that exposure to cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded," and in view of the support for these aspects and working examples in the specification, one of skill in the art would recognize that Applicants were in possession of the invention as claimed in claim 1 as amended. Applicants respectfully request reconsideration and withdrawal of the written description rejection of claim 1 as amended.

Claim 4 is rejected for lack of written description. The rejection is moot with respect to claim 4 because the claim is cancelled herein. However, the limitations of claim 4 have been amended into claim 1. To the extent that the rejection might be applied to claim 1 as amended, applicants respectfully traverse. The Office Action states:

> "Claim 1 is drawn to a method for the selection of a virus comprising (a) providing a virus encoding and displaying a fusion polypeptide comprising a polypeptide and a viral coat protein with a cleavable site, (b) exposing the virus to a cleaving agent, and (c) propagating the virus comprising intact fusion protein. Claim 4 is drawn to 'the method of claim 1 wherein cleavage impairs the ability of the polypeptide comprising the cleavage site to mediate the infection of the virus.' Therefore, viral infection is impaired and an intact fusion polypeptide can not be propagated unless the virus expressing intact fusion polypeptide is somehow protected from cleavage. In addition, how a polypeptide can mediate infection of a virus is not adequately described."

Applicants respectfully disagree.

The amendments to claim 1 make it clear that the cleaving agent only cleaves the cleavable site if the fusion polypeptide is not properly folded, such that exposing the plurality of virions to the cleaving agent selects against virions displaying fusion polypeptide that is not properly folded. It is clear from the amended claim language that virions displaying properly folded fusion polypeptides will not be cleaved, and can therefore be propagated – this is a primary basis of the selection method, as described at, e.g., page 8, lines 13-21.

With regard to descriptive support for "how a polypeptide can mediate infection of a virus," the role of viral coat proteins in the ability of a virus to infect host cells is very well

known in the art, both generally and with regard to coat proteins of numerous specific viruses. Further, the specification provides working examples of viral coat protein fusion polypeptides that mediate infection of host cells unless cleaved by a cleaving agent. (Simply to clarify the meaning of the claim language, it is noted that claim 1 as amended recites "infection *by* a said virion," rather than "infection *of* said virions" – see also below.)

In view of the amendments to claim 1 and the discussion above, the claim as amended is fully supported by the written description in the specification. Reconsideration and withdrawal of the written description rejection of claim 4 as it may apply to amended claim 1 is respectfully requested.

Rejections under 35 U.S.C. §112, Second Paragraph:

The Office Action rejects claim 1 and all dependent claims under 35 U.S.C. §112, second paragraph as incomplete for omitting essential steps. The Office Action states:

"The omitted steps are: Selecting virus which are resistant to cleavage. A selection step between steps (b) and (c) of the presently claimed invention is necessary since only properly folded fusion polypeptides would be protected from cleavage and thus allow propagation of virus encoding an intact fusion polypeptide. Fusion polypeptides that were not protected from cleavage during the exposure step would be cleaved and therefore no longer be intact."

Applicants respectfully disagree, as it is clear from the original language of the claim that the method is a selection method; if no virus is left intact there is no point in performing the method, so this is clearly not what is meant by the claim as originally presented. Nonetheless, in view of the amendments to claim 1 discussed above with regard to written description, this rejection is believed to be moot. The claim as amended specifically requires that the "cleaving agent only cleaves said cleavable site if said fusion polypeptide is not properly folded, such that said exposing selects against virions displaying fusion polypeptide that is not properly folded." Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

Claims 1 and 2 are rejected under 35 U.S.C. §112, second paragraph as indefinite for recitation of the phrases "a cleavable site located within a displayed polypeptide" (in claim 1) and "the cleavage site is located within the fusion polypeptide" (in claim 2). The Office Action states that the phrases are indefinite because it is not clear if the cleavable site can be found anywhere in the fusion polypeptide including non-displayed portions anchored in the phage capsid." Applicants respectfully disagree.

Claims 1 and 2 require that the virus comprises a cleavable site located within a displayed polypeptide. It is not clear how the language is indefinite because the claim does not specify whether "the cleavable site should only be in the displayed portion of the polypeptide or if the cleavable site can be anywhere in the fusion polypeptide including non-displayed portions anchored in the phage capsid." The specification describes parameters to consider and advantages of various placements of the cleavable site at, for example, page 4, lines 19-31 and page 6, lines 14-29. Thus, there is support for various locations for the cleavable site. One of skill in the art, given this description, would realize that placing the cleavable site in a location that has no potential to be exposed to a cleaving agent would be counter-productive. As such, the claims are not indefinite simply because they do not specify a precise location for the cleavable site. Further, breadth is not indefiniteness. *In re Miller*, 441 F.2d 689 (CCPA 1971); MPEP 2173.04. Finally, the definiteness requirement does not compel absolute clarity. Claims are only indefinite if they are "not amenable to construction" or "insolubly ambiguous." *Datamize, LLC v. Plumtree Software, Inc.*, 417 F.3d 1342, 1347-48 (Fed. Cir., 2005), citing *Novo Indus., LP v. Micro Molds Corp.*, 350 F.3d 1348, 1353 (Fed. Cir. 2003), *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003) and *Exxon Research & Eng'g Co. v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001). As discussed above, given the specification and ordinary skill in the art, one would know what is meant by the phrases "a cleavable site located within a displayed polypeptide" and "cleavage site is located within the fusion polypeptide." As such, Applicants respectfully request reconsideration and withdrawal of this indefiniteness rejection.

Claim 4 is rejected as indefinite for reciting the terms "impairs" and "mediate," which are said to be relative terms that render the claim indefinite. The rejection is moot due to the

cancellation of claim 4. It is noted that the phrase "infection of a virus" is stated as "infection *by* a said virion" when limitations of claim 4 are amended into claim 1. Further, to the extent that the rejection over the term "impairs" might be applied to claim 1 as amended, the specification states that "As used herein, 'impair' means to reduce; it thus includes but (sic) partial and complete prevention of infection of host cells by affected virus." As such, one of skill in the art would understand what is meant by the term. Reconsideration of the rejection as it might apply to claim 1 as amended is respectfully requested.

Claims 19 and 20 are rejected as indefinite for reciting "the bacteriophage is a helper bacteriophage used in conjunction with phagemids" (claim 19) and "the encapsidated nucleic acid of the bacteriophage is a phagemid and requires the use of a helper bacteriophage" (claim 20). The Office Action states that "it is not clear if two bacteriophage are present, e.g., one carrying the phagemid and one helper phage), if the helper phage is carrying the phagemid, as replication deficient bacteriophage carries the phagemid and a 'packaging' helper phage is required to package more phagemid nucleic acid, or if the host cell is transfected with the phagemid, infected with a 'packaging' helper phage, and then the helper phage encapsidates the phagemid nucleic acid, etc." The Office Action concludes "therefore the limitations of claims 19 and 20 are indefinite. Applicants respectfully disagree.

First, the limitation of claim 19 recited as "the method of claim 16 wherein the bacteriophage is a helper bacteriophage used in conjunction with phagemids" is definite as stated. One of skill in the art would know what a helper phage used in conjunction with phagemids is. Thus, one of skill in the art would understand the metes and bounds of the claim term, thereby satisfying the definiteness requirement.

Second, the plain language of claim 20 requires that the nucleic acid encapsidated by the bacteriophage recited in claim 19 (i.e., the helper bacteriophage), is a phagemid that requires the use of a helper bacteriophage. It is not clear where the lack of clarity arises. Nonetheless, to further clarify what is intended to be covered by the claim, claim 20 is amended to recite "in which the encapsidated nucleic acid of the *helper* bacteriophage is a phagemid and requires the

use of *said* helper bacteriophage." Reconsideration and withdrawal of the rejection is respectfully requested.

Claim 2 is rejected as indefinite for lack of proper antecedent basis for the limitation "the cleavage site" in the first line because "'cleavage site' suggests that cleavage has occurred (e.g., the act of cleaving) while 'cleavable site' suggests the property of being able to be cleaved only (e.g., capable of being cleaved)." Claim 2 is amended to recite "cleavable site" to agree more directly with the language of claim 1. Reconsideration and withdrawal of the rejection is respectfully requested.

Finally, claim 3 is rejected for lack of antecedent basis for the phrase "cleaved or uncleaved fusion polypeptide" in line 2. Applicants note that the phrase "cleaved or uncleaved fusion polypeptide" does not occur in claim 3. Nonetheless, in order to bring the language of claim 3 in line with that of amended claim 1, claim 3 is amended to recite "wherein after exposing said virus to said cleaving agent, a virion comprising uncleaved fusion polypeptide is separated from a virion comprising cleaved fusion polypeptide." The amendment adds no new matter. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102

Ladner et al.

The Office Action rejects claims 1-9, 11, 13-17 and 19-21 under 35 U.S.C. §102(b) as anticipated by Ladner et al., U.S. 5,223,409. The Office Action states, in part:

> Ladner *et al.* teach phage-displayed binding proteins (please refer to Abstract). Ladner *et al.* also teach a method comprising (a) preparing a variegated population of amplifiable genetic packages expressing a chimeric protein comprising a potential binding domain and an outer surface transport signal, (b) causing expression of the chimeric protein on the outer surface of the genetic packages, (c) contacting the packages with a target (e.g. ligand of present claims 13 and 15), (d) recovering and replicating at least one package bearing a successful binding domain (e.g. providing a virus, exposing the virus to a cleaving agent, and propagating the virus of present claim 1; please refer to column 10, lines 14-37).

The Office Action thus concludes that Ladner et al. anticipates the claimed invention. Applicants respectfully disagree.

Claim 1 as amended requires that the "cleavage of said cleavable site impairs infection by a said virion." In contrast, Ladner et al. teaches that cleavage of displayed fusion polypeptide results in phage *having* infective activity, rather than phage with impaired infective activity. Specifically, in a passage cited in the Office Action, the reference states:

> "GPs that display peptides having high affinity for the target may be quite difficult to elute from the target, particularly a multivalent target. (Bacteria that are bound very tightly can simply multiply in situ.) For phage, one can introduce a cleavage site for a specific protease, such as blood-clotting Factor Xa, into the fusion OSP protein so that the binding domain can be cleaved from the genetic package. Such cleavage has the advantage that all resulting phage have identical OSPs *and therefore are equally infective*, even if polypeptide-displaying phage can be eluted from the affinity matrix without cleavage. *This step allows recovery of valuable genes which might otherwise be lost. To our knowledge, no one has disclosed or suggested using a specific protease as a means to recover an information-containing genetic package or of converting a population of phage that vary in infectivity into phage having identical infectivity.* (Ladner '409 patent, column 73, lines 22-39; Emphases added)

That is, cleavage is taught in Ladner et al. as a means to enhance recovery of viruses that might otherwise be lost, rather than as a means of selecting against virions displaying fusion polypeptide that is not properly folded. Ladner's cleaved virions are propagated *better* than those that are not cleaved, in direct contrast to the situation in the methods encompassed by the amended claims. Further, because cleavage is used to render virions equally infective, the method taught by Ladner et al. does not involve "propagating a virion comprising intact fusion polypeptide" as required by claim 1.

Further, the Ladner et al. reference teaches the use of antibody binding to select for properly folded library members. See, in particular, column 11, lines 9-33. That is, the reference teaches a different approach from the method presently claimed for the selection of virus displaying properly folded polypeptides. This further emphasizes that the reference does not teach the exposure of a virus to a cleaving agent to select against virions displaying fusion polypeptide that is not properly folded, as required by the claims as amended.

In view of the above, Ladner et al. cannot anticipate the invention of claim 1 as amended, or of claims that depend from it. Reconsideration and withdrawal of the §102 rejection over Ladner et al. is respectfully requested.

Dower et al.

Claims 1-3, 5-7, 11, 13-17 and 21 are rejected as anticipated by Dower et al., U.S. 5,432,018. The Office Action states:

> Dower *et al.* teach screening and selecting bacteriophage expressing fusion proteins comprising peptides and coat proteins (e.g. bacteriophage of present claim 16; please refer to the Abstract and column 3, lines 49-62). Dower *et al.* claim a method for obtaining a bacteriophage encoding a substrate cleaved by a proteolytic enzyme comprising (a) transforming host cells with bacteriophage expression vectors encoding a fusion protein composed of a peptide fused to a ligand fused to a coat protein of filamentous bacteriophage, (b) cultivating the host cells suitable for expression and assembly of bacteriophage, (c) incubating the bacteriophage with a proteolytic enzyme wherein the displayed peptide is cleavable by the proteolytic enzyme, (d) contacting the bacteriophage to a receptor that binds the ligand, and (e) separating receptor-bound bacteriophage from unbound bacteriophage (e.g. providing a virus, exposing the virus to a cleaving agent, *propagating virus comprising intact fusion protein* of present claim 1, cleavage site located in the fusion polypeptide of present claim 2, separating virus expressing uncleaved and cleaved polypeptides of present claim 3, presence of a stabilizer of present claim 11, presence of ligand of present claim 13, selected by binding ligand of present claim 15, and a protease cleavable site of present claim 21; please refer to claims 1-2 of Dower *et al.*).

The Office Action thus concludes that Dower et al. anticipates the claimed invention. Applicants respectfully disagree.

Similarly to Ladner et al., the Dower et al. reference does not teach that "cleavage of said cleavable site impairs infection by a said virion," or that exposure to cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded," as required by claim 1 as amended. The Dower et al. reference relates to methods of obtaining a bacteriophage encoding a substrate cleaved by a preselected protrease enzyme, but does not teach that cleavage of the described bacteriophage fusion polypeptides impairs infection by the virion displaying the

fusion polypeptide. To the contrary, the method described in claim 1 of Dower et al. (specifically referred to in the Office Action for its disclosure), depends upon cleavage of a protease site on a bacteriophage coat protein fusion polypeptide to permit receptor binding by the expressed ligand fusion polypeptide. The fusion protein taught by Dower et al. is "composed of a random peptide fused to a known ligand for a receptor, which known ligand is in turn fused to a coat protein of a filamentous bacteriophage wherein .... said ligand will not bind said receptor when said ligand is fused to said random peptide." Ligand binding by the fusion polypeptide permits recovery of bacteriophage that encode fusion polypeptide with a cleavable site, but cleavage by the protease *must* occur for the ligand binding to occur. That is, the method taught by Dower et al. does not involve "propagating a virion comprising intact fusion polypeptide," as required by claim 1. Because bacteriophage are recovered only if they have been cleaved, the teachings of Dower et al. are essentially the opposite of the requirements of claim 1 as amended. Applicants respectfully request reconsideration and withdrawal of this §102 rejection over Dower et al.

Rejections under 35 U.S.C. §103

Ladner et al. in view of Smith

Claims 1-9, 11 and 13-21 are rejected under as obvious under 35 U.S.C. §103, over a combination of Ladner et al. and the G.P. Smith reference (Science 228: 1315-1317 (1985). The Office Action repeats the summary of Ladner et al. recited with respect to novelty, then states:

> However, while Ladner et al teach that the protein binding domain can be fused to gene III at the site used by Smith, Ladner *et al.* does not specifically describe the site used by Smith as the second and third domain of gene 3.
>
> Smith teaches that a foreign sequence can be inserted between the F pilus binding domain and the domain that is buried in the virion of pIII without disrupting pIII function (e.g. second and third domains of gene 3 of present claim 18; please refer to page 1315).
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teaching of Ladner *et al.* with the specific location of the peptide between the second and third domains of the pIII coat protein taught by Smith.
>
> One having ordinary skill in the art would have been motivated to do this because the insertion of a sequence between the second and third domains of pIII did not disrupt pIII function (please refer to Smith page 1315, first column and

Figure 1). Furthermore, the location of the peptide and pIII in the fusion polypeptide would be a design choice as long as the fusion polypeptide would be functional.

Applicants respectfully disagree.

The deficiencies of the Ladner et al. reference relative to the claims as amended are discussed above with respect to novelty. The Smith reference fails to remedy these deficiencies with respect to the invention as claimed in, e.g., claim 1 as amended. Specifically, the Smith reference does not teach that "cleavage of said cleavable site impairs infection by a said virion," nor does it teach that exposing the virus to a cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded" as required by claim 1 as amended.

Further, as noted above, the Ladner et al. reference teaches the use of antibody binding to identify or enrich for library members that are properly folded. Not only does Smith not remedy the deficiencies of Ladner et al., but in view of Ladner's teaching of antibody selection for folding, there is also no motivation to modify the methods taught by Ladner et al. to include exposure to a cleaving agent in order to select against virions displaying fusion polypeptide that is not properly folded.

In view of the above, the combination of Ladner et al. with Smith fails to teach or suggest every element of the invention as presently claimed. As such, the claimed invention cannot be obvious over any combination of these references. Applicants respectfully request reconsideration and withdrawal of the §103 rejection over these references.

Dower et al. in view of Breitling et al.

Claims 1-3, 5-7, 11, 13-17 and 19-21 are rejected as obvious under 35 U.S.C. §103 over a combination of Dower et al. and Breitling et al., U.S. 5,849,500. The Office Action summarizes the teachings of Dower et al. as in the novelty rejections, but states that "Dower et al. does not teach the use of phagemid and helper bacteriophage." With respect to Breitling et al., the Office Action states:

> Breitling *et al.* teach a phagemid that expresses an antibody fused to pIII protein wherein the phagemid is suitable for selecting specific antibodies from large gene libraries (please refer to the Abstract). Breitling *et al.* also teach that peptides can be inserted between two domains of pIII (please refer to column 1, lines 43-51). Breitling *et al.* further teach the use of the phagemid pSEX and the phage fd to express the antibody-pIII fusion protein (please refer to column 4, lines 55-64). In addition, Breitling *et al.* teach the use of a protease cleavage site (please refer to column 3, lines 17-20).
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the phage-displayed library of Dower *et al.* with the antibody-pIII fusion protein expressed by phagemid with a helper phage of Breitling *et al.*
>
> One having ordinary skill in the art would have been motivated to do this because Breitling *et al.* teach that larger inserts have an adverse effect on the infectivity function of pIII and there is a risk that phage libraries will become dominated by deletion mutants after library amplification (please refer to column 2, lines 3-1 5). Furthermore, Breitling *et al.* teach that the phagemid is propagated as a plasmid and is not under selection pressure to remove antibody DNA (please refer to column 2, lines 19-36).
>
> There is a reasonable expectation of success in the modification of the phage-displayed library of Dower *et al.* with the teachings of Breitling et at because of the example in Breitling *et al.* showing the expression of antibody-pIII fusion protein from a phagemid with a helper bacteriophage (please refer to columns 3-5 and Figure 2 of Breitling *et al.*).

Applicants respectfully disagree.

The deficiencies in the Dower et al. teachings with respect to the claimed invention are discussed above. As discussed above, cleavage is necessary for virus propagation in the methods described by Dower et al., whereas, in the presently claimed methods, cleavage impairs infection, and exposure to cleaving agent selects against virions displaying fusion polypeptide that is not properly folded. The Breitling et al. reference fails to remedy these deficiencies of the Dower et al. reference. Specifically, the Breitling et al. reference does not teach that "cleavage of said cleavable site impairs infection by a said virion" (which would also directly contradict the primary Dower et al. reference) nor does it teach that exposing the virus to a cleaving agent "selects against virions displaying fusion polypeptide that is not properly folded" as required by claim 1 as amended. Thus, the combination of Dower et al. with Breitling et al. fails to teach or suggest every element of the invention as presently claimed. As such, the claimed invention

cannot be obvious over any combination of these references. Applicants respectfully request reconsideration and withdrawal of the §103 rejection over these references.

Dower et al. in view of Breitling et al. and Smith:

Claim 18 is rejected as obvious over a combination of Dower et al. and Breitling et al. as applied to claims 1-3, 5-7, 11, 13-17 and 19-21, further in view of Smith. The Office Action states:

> The combine (sic) teachings of Dower *et al.* and Breitling *et al.* are obvious over the presently claimed invention since it is obvious to utilize phagemids for expressing large polypeptides on the surface of phage as discussed in section 36 above. However, the combine teachings of Dower *et al.* and Breitling *et al.* differ from the presently claimed invention by failing to the insertion of the polypeptide between the second and third domains of gene 3.
>
> Smith teaches that a foreign sequence can be inserted between the F pilus binding domain and the domain that is buried in the virion without disrupting pIII function (e.g. second and third domains of gene 3 of present claim 18; please refer to page 1315).
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the teachings of the bacteriophage-displayed fusion polypeptides of Dower *et al.* and Breitling *et al.* with the specific location of the peptide between the second and third domains of the pIII coat protein taught by Smith.
>
> One having ordinary skill in the art would have been motivated to do this because the insertion of a sequence between the second and third domains of pIII did not disrupt pIII function (please refer to Smith page 1315, first column and Figure 1). Furthermore, the location of the peptide and pIII in the fusion polypeptide would be a design choice if the fusion polypeptide would be functional.
>
> There is a reasonable expectation of success in the combination of Dower *et al.*, Breitling *et al.*, and Smith because of the data in Figure 1 of Smith showing that a sequence can be inserted between the second and third domains of pIII wherein pIII is still functional.

Applicants respectfully disagree.

The deficiencies of the Dower et al. and Breitling et al. references with respect to the independent claim 1 as amended are discussed above. The Smith reference also fails to remedy these basic deficiencies. Therefore, no combination of Dower et al., Breitling et al. and Smith

can render obvious the claimed methods. Applicants respectfully request reconsideration and withdrawal of the §103 rejection over these references.

In view of the above, Applicants submit that all issues raised in the Office Action have been addressed. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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